RECEIVED
CENTRAL FAX CENTER
OCT 2 8 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mundy *et al.*
Serial No. : 09/805,840
Filed : March 13, 2001
Title : METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS

Art Unit : 1644
Examiner : Maher M. Haddad, Ph.D.

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND DECLARATION OF DR. BLAKE PEPINSKY UNDER 37 C.F.R. §1.132

I, Blake Pepinsky, a citizen of U.S.A. residing in Arlington, MA, hereby declare as follows:

1. I am Director of Protein Chemistry at Biogen Idec Inc. I received my doctorate in Biochemistry from Cornell University, where I also completed postdoctoral training. I have over 20 years experience in the field of antibody therapeutics and small molecule therapeutics. I have published over 120 scientific articles, including 24 articles specifically on integrin studies. I serve or have served as an ad-hoc reviewer for the editorial boards of over a dozen different scientific journals.

2. I have reviewed the above-referenced patent application and the references discussed herein.

3. I have been advised and understand that the Examiner has rejected claims 1, 2, 4, 5, 9, 31, 32, 40 and 42-44, which are directed to methods of treating multiple myeloma with an anti-α4 integrin antibody, as unpatentable in view of a combination of two references: U.S. Patent No. 6,495,525 to Lee *et al.* ("Lee") and PCT Publication No. WO 95/19790 ("Bendig"). The Examiner argues that, at the time of priority (September 14, 1998), one of ordinary skill in the art would have been motivated

to substitute the anti-α4 antibodies taught by Bendig for the small molecule oMePUPA-V taught by Lee, to treat multiple myeloma.

4. At the time of filing, a practitioner of ordinary skill in this field would not, for numerous reasons, have believed that oMePUPA-V would be interchangeable with anti-α4 integrin antibodies to treat multiple myeloma. There are many structural and functional differences between oMePUPA-V and an anti-α4 integrin antibody. *E.g.*, the two do not bind to the same set of targets (*see* paragraphs 5 and 6 below), and an example in Lee shows explicitly that they are not interchangeable (*see* paragraph 7 below).

5. There are numerous structural and functional differences between oMePUPA-V and anti-α4 integrin antibodies that would have made substitution unpredictable. It would have been unpredictable that an antibody against α4 integrins would have the same effect as any anti-VLA-4 (α4/β1 integrin) small molecule, much less oMePUPA-V. Antibodies are completely different than small molecules. In the first place, antibodies as a class of agents are vastly different in size than small molecule drugs such as oMePUPA-V. Due to its small size, a small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where by that very nature it may act as either an agonist or an antagonist. In contrast, antibodies are large molecules and, while they may bind to a particular epitope on a target, they effectively cover a large surface area and thereby act to block a biological pathway through steric hindrance, as opposed to binding a specific active site or pocket. In many cases, some target pockets are simply not accessible to antibodies. This is the case in the present situation. That is, oMePUPA-V binds at the ligand binding site and therefore may act as an agonist. In contrast, none of the existing anti-α4 integrin antibodies bind directly at the ligand binding site. For this reason alone, a skilled practitioner would not have believed oMePUPA-V to be interchangeable with an anti-α4 integrin antibody.

6. In addition, an anti-α4 integrin antibody would not have been expected to have the same *in vivo* effect as oMePUPA-V in particular because anti-α4 integrin antibodies have a different specificity than oMePUPA-V. Lee teaches that oMePUPA-V is highly specific for VLA-4 (having α4/β1 subunits) but does not act on α4/β7 integrin (*see* Lee, column 7, lines 39-42; and column 25, lines 33-34). In contrast, the α4 integrin antibodies recited in the claims can bind both α4/β1 and α4/β7, implicating an additional integrin pathway. The broader specificity of an anti-α4 integrin, compared to oMePUPA-V, would have made it unpredictable that an anti-α4 antibody would have the same effect as oMePUPA-V *in vivo* at all, much less have the same applicability across such a broad range of disorders and particularly against any one particular listed disorder, such as multiple myeloma.

7. Furthermore, Lee itself demonstrates that oMePUPA-V and an anti-α4 integrin antibody are not interchangeable. In Example 3, Lee compared the activities of oMePUPA-V and an anti-VLA-4 antibody in animal models of delayed type hypersensitivity (*see* column 22, lines 6-52). In this Example, sheep red blood cells were injected into the rear footpads of mice, and the independent effects of oMePUPA-V and an anti-VLA-4 antibody on footpad swelling were measured. In this side-by-side comparison, the two types of molecules worked very differently. Lee states that enteral administration of oMePUPA-V did not inhibit footpad swelling. In contrast, Lee states that the anti-VLA-4 antibody administered intraperitoneally inhibited swelling by approximately 30%. Thus, Lee specifically teaches that an anti-VLA-4 antibody and oMePUPA-V are not interchangeable. As such, a skilled practitioner, at the time of filing, would not have believed oMePUPA-V to be interchangeable with an anti-α4 integrin antibody to treat multiple myeloma.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements

and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 10/25/05

Blake Pepinsky
Dr. Blake Pepinsky

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21189266.doc